Citizen Petition
No. 98P-0434/CP1/PSA1

nds International

Longwood Corporate Center South
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March 12, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, (Room 10-61)
Rockville, MD 20857

Re: CITIZEN PETI TION
Estradiol Transdermal System
Docket No. 98P-0434/CP1/PSA1

Dear Sir or Madam,

This is an "Addendum" to the Letter/Report" dated March 10, 1999. The original letter failed to include the "Curriculum Vitae" cited in 2nd paragraph of my report.

Please append the "Curriculum Vitae" to the original report.

Sincerely,

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98P-0434

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Re: CITIZEN PETI TION
Estradiol Transdermal System
Docket No. 98P-0434/CP1/PSA1

Dear Sir or Madam,

This letter and brief report is to serve notice that I support the "Citizen Petition" filed jointly by BERLEX Laboratories, Inc. ("Berlex") and 3M Pharmaceuticals ("3M") on June 12, 1998 concerning "Estradiol Transdermal System".

In support of this Citizen Petition, I am including specific recommendations and have appended my "curriculum vitae". Although I am reasonably well known to the Agency, a brief summary of my past and present activities needs to be cited for the record.

I have been involved in pharmaceutical research for more than 40 years. During the past 40 years, my career has involved 12 years with the "pharmaceutical industry" initially as a research scientist (Pfizer and Bristol Myers) and thereafter as Head of Pharmacokinetics (Bristol Myers). I devoted ten (10) years of my scientific career with the Food and Drug Administration (1973 – 1983) as Director of the Division of Biopharmaceutics. For the past 32 years I have been involved in "Biopharmaceutics Research" more specifically the area encompassing "bioavailability and pharmacokinetics" of drugs. I have authored numerous scientific articles in the field of "Clinical Pharmacology", "Bioavailability" and "Pharmacology".

As Founder and Director of the Division of Biopharmaceutics, Food and Drug Administration, I was senior author of the "*Proposed Rulemaking on Human Drugs*" promulgated in the Federal Register on June 20, 1995 proposing to establish "*Bioequivalence Standards*" for medically important drugs. I was also senior author of the "Final Order" establishing a "*Bioequivalence Requirements and In Vivo Bioavailability Procedures - for Drug Products*", - Part CFR 320 promulgated on January 7, 1977 (*Federal Register, Vol.42, No. 5 1624 – 1653, January 7, 1977*). This "Final Order" is the basis of current standards at FDA and specifically cited in the "Waxman-Hatch Act", (Patent Restoration Act) of 1984 as a basis for establishing "Therapeutic Equivalence" of generic drugs.

Since leaving the Agency in 1983, I have directed the conduct of 100's of "bioavailability studies" involving "new drugs" and "generic drugs" including that of estradiol.

During my tenure as Director of the Division of Biopharmaceutics, I have always advocated the "*need for the highest public standards*" for medically important drugs. It is to that end that I am addressing these comments.

More specifically I fully endorse the concept that

1. All "medically important drugs" should have the highest standard to assure the bioavailability and reproducibility of the dosage form;
2. Such standards should be a "public standard" established either through "Rulemaking" and/or have underwent "scientific scrutiny";
3. The "standards" for specialized dosage form i.e., controlled release dosage forms, should be adequate so as to assure the reproducibility (in terms of bioavailability and/or clinical efficacy) of the dosage;
4. The standards should be based upon the "highest standard" scientifically feasible based upon "good science".

For Estradiol Transdermal System(s) and/or drug delivery I fully endorse the need for the following:

1. Use of "steady-state" design to establish "bioequivalence";

The use of single-dose studies involving "controlled release dosage forms" should be limited to the establishment of "*dose-proportionality*", for the additional purpose of ruling-out "*dose-dumping*" and for the purpose to developing "*in vitro - in vivo correlations*". Although I support the concept that a "single dose" design is adequate to define the rate of absorption and to rule-out "dose-dumping" for a controlled-release dosage forms such as "*Estradiol Transdermal System*", it is totally inadequate to establish the "*bioequivalence*" and/or "*therapeutic equivalence*" of a controlled release dosage form. (The latter position was clearly enunciated in the Final Order of January 7, 1977 (see CFR 320.25 (f) (iii)).

Furthermore, the single dose design, for it to achieve its intended goals (described above) needs to include adequate early time-points to rule out "dose-dumping" and adequate sampling of plasma levels so as to define the "elimination half-lives" to further permit determination of "absorption rate" using the "Wagner-Nelson Method" (1963).

2. The use of "single dose design" is totally inadequate for Estradiol Transdermal System(s);

Single dose design involving estradiol transdermal systems are in my opinion "inadequate" to assure the "bioequivalence" and "therapeutic equivalence" of such dosage forms due to the great variability of "endogenous" estradiol" (E2) and "estrone" (E1) at baseline following "washout". Several years ago, I submitted to the FDA clinical studies in "post-menopausal" women which showed that following a single week "wash-out" period, the endogenous "estradiol" levels (E2) varied greater than 50% and at times up to 154% in any given women at "baseline"when compared to the previous week levels.

To superimpose a single dose regimen upon such a "variable" baseline and to expect "bioequivalence" is sheer nonsense even if one attempts to perform a "co-variate analysis" of the data taking into account the variable "baseline".

3. The use of "single dose design" is inadequate for estradiol transdermal systems to assure its reproducibility in a clinical setting;

A "single-dose" design fails to demonstrate the "reproducibility" of the dosage form in a clinical setting. Since there is a "high probability" that substitution of a "generic" dosage form would take place in clinical setting which involves substitution under "steady-state" condition, it is mandatory that the drug delivery be shown to perform under such clinical setting;

4. The use of "multiple dose" "steady-state" design is well known to be the "highest standards" for "controlled release dosage forms" such as the "Estradiol Transdermal Systems";

As clearly stated in the January 7, 1977 Final Order "*Bioequivalence Requirements and In Vivo Bioavailability Procedures - for Drug Products*", - (Part CFR 320.25 (f), *Federal Register, Vol.42, No. 5 1624 – 1653, January 7, 1977*), the "multiple dose" "steady-state" design is the "highest standard" for "controlled drug delivery. It is my scientific opinion that there is an absolute need for a "generic' form of a controlled release dosage form i.e., "Estradiol Transdermal Systems" to demonstrate that it can achieve/maintain the same "steady state" as that of the innovator that it purports to mimic.

The best scientific approach involves the use of a "multiple-dose", "steady-state" design without a "wash-out". A "generic" "Estradiol Transdermal Systems" should be required to demonstrate that it can achieve/maintain the same "equivalent" steady-state as that of the "innovator". Failing that, the drug product(s) may be "approvable", but cannot be deemed "equivalent".

5. Multiple-dose studies establishing "bioequivalence" at various sites should be required of all manufacturer to support "Labeling";

During the past few years I became aware of significant differences in the "steady-state" bioavailability of "Estradiol Transdermal Systems" when administered on the "buttocks" vs. "abdomen". The latter findings at time ranging from 15-25% in differences is not too surprising if one considers the physical-chemical parameters that inter-play particularly when combined with differences in "lipophilicity" and "blood-flow" at the different body sites.

From a "regulatory perspective", the Agency currently mandates the conduct of "bioavailability" studies to support "Labeling" at different sites. I fully endorse this "FDA policy", but in my opinion the same "policy" needs to be applied of the "generic" firms. Failing to do so can only lead to "uncertainty" concerning the "therapeutic equivalence" of the dosage forms in question (particularly since significant differences have been noted with the currently approved innovator dosage forms).

This issue is very similar to the "well known" "food effect" that was manifested with theophylline dosage forms in the mid 1980's. In the latter case, experience tells us that such studies should have been mandated. In all likelihood, the same results could manifest itself if the Agency fails to endorse this "policy".

6. "Bioequivalence" studies should be performed in accordance to "dosage instruction" without use of artificial adhesives;

In more recent times, I have become aware of the fact that in the conduct of "bioequivalence" purporting to support "therapeutic equivalence" of the transdermal dosage, artificial means of securing the patch i.e., 'use of adhesives" are employed in such trials. In my opinion, this flies in the face of "Good Regulatory Science" since in no way does such a study mimic the clinical setting that will prevail once the dosage form is "approved". I support the current Citizen Petition that advocate to test the drug delivery systems as they will be used clinically.

7. "Bioequivalence" parameters should consist of $AUC\tau$, C_{max}, C_{min} and Fluctuation index $((C_{max} - C_{min})/(C_{ave})$;

It is my scientific opinion that "therapeutic equivalence" of controlled release dosage forms e.g. "Estradiol Transdermal Systems" mandates comparison of "steady-state" parameters described above. Proof of "bioequivalence" requires demonstration that equivalent "steady-state" were in fact achieved. The most sensitive parameter is that of C_{min} and not $AUC\tau$. The Agency should mandate statistical approaches that establishes that steady-state was in fact established and/or maintained for both dosage forms and that such steady-state C_{min} are "equivalent" (by comparison of 90% C.I. limits). A pre-requisite for the latter requires a minimum of three (3) Cmin values to be at "steady-state.

8. "Bioequivalence" testing should involve the most sensitive analytical method known;

Given the "variable baseline" of endogenous estradiol (E2) and estrone (E1), the Agency should mandate the use the most sensitive analytical assay. The Agency should require either the use of GC-MS assays or an analytical method sufficiently specific so as to measure accurately and specifically the levels of E2 and E1 in serum or plasma.

9. The "Guidance" and/or "Guideline" for Estradiol Transdermal System should be a "public standard" and thus should be established in a "public forum";

Given the "medical import" of this drug and the scientific controversy concerning the '*Bioavailability standard*', I recommend that a "Guideline" be established in a "public forum" either through "Rulemaking" as defined in the January 7, 1977 Final Order "*Bioequivalence Requirements and In Vivo Bioavailability Procedures*" or by convening the Agency's "Generic Advisory Board" to fully discuss the various scientific approaches for establishing "Bioequivalence" of Estradiol Transdermal System.

In this report, I have dealt with the most pressing scientific issues concerning "Estradiol Transdermal Systems" and not with the minutia in how to best conduct the study. I personally believe that there are a variety of "multiple dose design" that could be employed and these are best left to the Advisory Board or better yet to the investigators. However, the scientific opinions expressed herein concerning "controlled release dosage forms" are based upon extensive studies performed by myself and/or colleagues during the past 10 years with many drugs of similar behavior, i.e. L-carnitine, B-carotene, potassium and estradiol (all having highly variable endogenous serum levels).

I hope that my recommendations are of value to the Agency in their 'unending" struggle to establish "public standards". In the event that the "Generic Drug Advisory Board" is convened to establish a "Bioequivalence Guideline", I would appreciate being notified and I would gladly participate in such a "scientific debate".

I remain,

Sincerely,

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BERNARD E. CABANA, Ph.D.

EDUCATION:

Ph.D.:	Pharmacology, State University of New York at Buffalo, College of Medicine, Buffalo, New York, 1967.
Thesis Title:	A Study of the Pharmacological Interaction of Ethanol with Chloral Hydrate.
M.A.:	Chemistry, Connecticut College, New London, Connecticut, 1963.
B.S.:	Chemistry, Providence College, Providence, Rhode Island, 1958.
Diploma:	Assumption Preparatory School, Worcester, Massachusetts, 1953.

EXPERIENCE:

1994 - present President and Founder of NDS International, Inc.
Kennett Square, Pennsylvania

1994 - present President and Founder oF IDR Delaware, Inc.
Kennett Square, Pennsylvania

1993 - 1994 President, Institute for Human Pharmacodynamics
Paoli, Pennsylvania

1993 - 1994 Vice President, Great Valley Pharmaceuticals
Malvern, Pennsylvania

1992 - 1996 Director, Great Valley Pharmaceuticals
Malvern, Pennsylvania

1988 - 1994 Chairman of the Board and co-founder of New Drug Services, Inc.
Kennett Square, Pennsylvania

1987 - 1993 President and Founder of IDR Laboratory and Clinic,
Gaithersburg, Maryland

1984 - 1995 President and Founder of IDR Limited,
Basel, Switzerland

1983 - 1997 Chairman and Founder of International Drug Registration, Inc.,
Gaithersburg, Maryland

1973 - 1983 The U.S. Food and Drug Administration, National Center for Drugs and Biologics, Rockville, Maryland.

- •1979 - 1983 - Appointed to Senior Executive Service by Secretary Califano, July 1979.
- •1974 - 1983 - Director, Division of Biopharmaceutics.
- •1973 - 1974 - Special Assistant to the Director, Office of Scientific Coordination.

1967 - 1973 Bristol Laboratories Medical Research Laboratories, Syracuse, New York.

- •1970 - 1973 - Head, Pharmacokinetic & Toxicokinetic Section Dept. of Drug Metabolism and Pharmacokinetics,
- •1967 - 1970 - Senior Research Scientist in Pharmacology.

1963 - 1967 New York Research Foundation: S.U.N.Y. at Buffalo, Buffalo, New York. Research Fellow

1958 - 1963 Chas. Pfizer Medical Research Laboratories, Groton, Connecticut. Research Scientist in Chemical Pharmacology & Enzymology

AWARDS/ACHIEVEMENTS:

Recipient of the U.S. Food and Drug Administration **"1981 FDA Award of Merit."**

Recipient of the **"Wood Badge"** from the Boy Scouts of America, 1980.

Recipient of the U.S. Food and Drug Administration **"1977 FDA Award of Merit."**

U.S. PHS Fellowship/Traineeship in Pharmacology at S.U.N.Y., College of Medicine, 1967-1973.

PROFESSIONAL SOCIETIES AND ORGANIZATIONS

American Society for Clinical Pharmacology and Therapeutics, 1977 - present.

The New York Academy of Sciences, 1992 - present.

Controlled Release Society, 1984 - present.

American Association of Pharmaceutical Scientist 1992 - present.

Academy of Pharmaceutical Sciences, American Pharmaceutical Association, 1976 - 1992.

Federation Internationale Pharmaceutique, 1978 - 1994

American College of Neuropsychopharmacology Task Force on **"CNS Toxicity of Pharmacotherapy,"** 1981-1985.

American College of Neuropsychopharmacology **"Task Force on Bioavailability "** (Secretary), 1975-1981.

Academy of Pharmaceutical Sciences "Dissolution/ Bioavailability Task Force," 1975-1983.

American Society of Microbiology, 1968-1978.

American Chemical Society, 1958-1973.

Editorial Board of Antimicrobial Agents and Chemotherapy, 1973-1976.

International Union Pharmacology, 1970-1973.

OTHER ORGANIZATIONS:

Conewago Anglers Association, 1993-present.

Montana Wildlife Federation, 1997 - present.

Trout Unlimited, 1997 - present.

Potomac Appalachian Trail Club, 1982-.1994

Boy Scouts of America, 1967-1984.
Order of the Arrow, Brotherhood, 1979-1984.
Boy Scouts of America, Woodbadge, 1982

PUBLICATIONS:

Adams, M.P., Cabana, B.E., Conlon, J., and Atkins T.J., **Inapplicability of Log-Transformation in Bioequivalence Assessment of Bimodally and Symmetrically Distributed Parameters** (Abstract) presented at American College of Clinical Pharmacology Annual Meeting , September 18-20, 1997 (in press)

Cabana, B.E.,Adams, M. P., Conlon, J., and Sobeki, J., **Effect of "Gender " and "Polymorphism" on the Assessment of Bioequivalence of Nitroglycerin Patches**. Pharm Res. (Suppl.) 13 (9): 460, 1996

Vetticaden, S.J., Prasad, V.K., Cabana, B.E., Purich, E.D., Jonkman, J.H.G., De Zeeuw, R., Leeson, L.J., and Braun, R.L.: ***Phenotypic differences in dextromethorphan metabolism.*** Pharm. Res 6(1): 13-19, 1989.

Vetticaden, S.J., Schary, W.L., Purich, E.D., Cabana, B.E., Karnes, H.T., Barr, W.H.,: ***Bioavailability and pharmacokinetics of toresamide in young and elderly healthy subjects.*** Pharm. Res. 5(10): S-167, 1988.

Prasad, V.K., Vetticaden, S.J., Purich, E.D., Schary, W.L., Cabana, B.E., Karnes, H.T., Barr, W.H.,: ***Dose proportionality study of toresamide - A loop diuretic.*** Pharm. Res. 5(10): S-217, 1988.

Cabana, B.E., Purich, E.D.: ***Establishing bioavailability and bioequivalence of diazepam formulation.*** Integr. Psychiatry 3: 79S-83S, 1985.

Cabana, B.E.: ***Bioavailability and pharmacokinetics in drug development.*** (In Plenum Press), pp. 113-132, ***Pharmacokinetics - A modern view.*** Ed. L.S. Benet, Levy, G., Ferrailo, B.L., 1984.

Cabana, B.E.: ***In vitro drug product dissolution testing correlation of results to in vivo bioavailability parameters***, Chapter 3, pp. 91-111, in Controlled Drug Bioavailability, Vol. 2: Bioavailability Methodology and Regulations, Ed. V.F. Smolen, L.A. Ball, John Wiley & Sons, New York, 1984.

Cabana, B.E.: ***Regulatory considerations in transdermal controlled medication.*** Drug Development and Ind. Pharm., 9 (4) 707-724, 1983.

Cabana, B.E., Chien, Y.W.: ***Regulatory considerations in controlled release medication,*** in ***Novel drug delivery systems.*** Edited by Chein, Y.W., Marchel Dekker, New York, N.Y., 1982.

Prasad, V.K., Rapaka, R.S., Knight, P., Cabana, B.E.: ***Dissolution medium - A critical parameter to identify bioavailability problems of furosemide tablets.*** International Journal of Pharmaceutics, 11: 81-90, 1982.

Rapaka, R.S., Roth, J. Viswanathan, C.T., Goehl, T., Prasad, V.K., Cabana, B.E.: ***Improved method for the analysis of furosemide in plasma by high-performance liquid chromatography.*** Journal of Chromatography, 227: 463-469, 1982.

Ringhand, H.P., Ritschel, W.A., Meyer, M.C., Straughn, A.B., Cabana, B.E.: ***Bioavailability of propylthiouracil in humans.*** J. Pharm. Sci., 1982.

Shah, V.P., Keys, C.A., King, D.M., Prasad, V.K., Cabana, B.E.: ***Thiazides XIII: Dissolution testing: A bioavailability predictor for benzthiazide tablets.*** Biopharmaceutics and Drug Disposition, 3: 283-285, 1982.

Shah, V.P., Knight, P., Prasad, V.K., Cabana, B.E.: ***Thiazides IV: Comparison of dissolution with bioavailability of chlorothiazide tablets.*** Journal of Pharmaceutical Sciences, 71: 822-824, 1982.

Hunt, J.P., Shah, V.P., Prasad, V.K., Schuirmann, D.J., Cabana, B.E.: ***Dissolution profiles and specification for dihydroergotoxine sublingual tablets using a new in vitro method.*** Journal of Pharmaceutical Sciences, 70: 796-798, 1981.

Purich, E.D., Cabana, B.E.: ***Generic phenytoin versus dilantin for one-a-day dosing.*** American Journal of Hospital Pharmacy, Vol. 38, August, 1981.

Rapaka, R.S., Roth, J., Goehl, T.J., Prasad, V.K., Cabana, B.E.: ***Anticoagulants interfere with analysis for furosemide in plasma.*** Clinical Chemistry, Col. 27, No. 8, 1981.

Shah, V.P., Hunt, J., Prasad, V.K., Cabana, B.E.: ***Comparison of plasma and urine analyses for thiazides in bioavailability/bioequivalence study.*** Journal of Pharmaceutical Sciences, 70: 833-835, 1981.

Shah, V.P., Lee, J., Hunt, J., Prasad, V.K., Cabana, B.E., Foster, T.: ***Thiazides V: Comparative bioavailability studies on 500 mg chlorothiazide tablets and solution.*** Current Therapeutic Research, 29: 802-814, 1981.

Shah, V.P., Lee, J., Hunt, J., Prasad, V.K., Foster, T., Cabana, B.E.: ***Thiazides VII: Lack of dose-proportional absorption-elimination of chlorothiazide.*** Current Therapeutic Research, 29: 823-837, 1981.

Cabana, B.E.: ***Bioequivalence and in vitro testing of drug formulations.*** Towards Better Safety of Drugs and Pharmaceutical Products, Ed. D.D. Breimer, p. 301-322, Elsevier/North Holland Biomedical Press, 1980.

Cabana, B.E.: ***Biopharmaceutical issues in drug product selection: FDA's point of view, health care delivery in the current United States regulatory environment, Part 1.*** Texas Southern University School of Pharmacy, Houston, Texas, March, 1980; The Apothecary, 92: 30, 1980.

Heck, H. d'A., Buttrill, S.E., Flynn, N.W., Dyer, R.L., Anbar, M., Cairns, T., Dighe, S.V., Cabana, B.E.: ***Bioavailability of imipramine tablets relative to a stable isotope-labeled internal standard: Increasing the power of bioavailability tests.*** Journal of Pharmacokinetics and Biopharmaceutics, Vol. 7, No. 3, 223-248, 1979.

Cabana, B.E.: ***Bioavailability/bioequivalence requirements for drugs in the U.S.A..*** ACTA Pharmaceutica Suecica, Volume 15, No.4, 1978.

Shah, V.P., Prasad, V.K., Cabana, B.E., Sojka, P.: ***Thiazides II: New pharmacokinetic findings on chlorothiazide using HPLC analysis.*** Current Therapeutic Research, 24: 366-379, 1978.

Cabana, B.E.: ***Bioavailability/Bioequivalence.*** Food and Drug Cosmetic Law Journel, 32 (Noll) 512-526, 1977.

Cabana, B.E., Douglas, J.F.: ***Bioavailability-pharmacokinetic guidelines for IND development, industrial bioavailability & pharmacokinetics.*** Martin & Doluisio, Univ. of Texas Press, May 1977.

Cabana, B.E., Kumkumian, C.: ***A view of controlled release dosage forms, industrial bioavailability & pharmacokinetics.*** Martin & Doluisio, Univ. of Texas Press, May 1977.

Cabana, B.E.: ***Applications and contributions of animal models in drug bioavailability.*** Psychopharmacology Bulletin, 12: 51-52, 1976.

Cabana, B.E.: ***Importance of biopharmaceutics and pharmacokinetics in clinical medicine.*** Arzneimittel-Forschung, 26: 151-158, 1976.

Cabana, B.E., Dittert, L.W.: ***Drug absorption and disposition as monitors of safety and efficacy.*** J. Pharmacok. & Biopharm., 3: 143-158, 1975.

Cabana, B.E., Van Harken, D.R., Hottendorf, G.H.: ***Comparative pharmacokinetics and metabolism of cephapirin in laboratory animals and humans.*** Antimicrobial Agents and Chemotherpay, 10: 307-317, 1975.

Cabana, B.E., Van Harken, D.R., Hottendorf, G.H., Doluisio, J.T., Griffen, W.O., Bourne, S.W.A., Dittert, L.W.: ***The role of kidney in the elimination of cephapirin in man.*** J. Pharmacok. & Biopharm., 3: 419-438, 1975.

Hottendorf, G.H., Van Harken, D.R., Madissoo, H., Cabana, B.E.: ***Pharmacokinetic considerations in toxicology.*** Excerpta Medical International Congress Series, European Society of Toxicology, 17: 255-261, 1975.

Cabana, B.E., Gessner, P.K.: ***The kinetic of chloral hydrate metabolism and the effect thereon of ethanol.*** J. Pharmacol Exp. Ther., 174: 260-275, 1970.

Cabana, B.E., Willhite, L., Bierwagen, M.E.: ***Pharmacokinetic evaluation of the oral absorption of different ampicillin preparation in beagle dogs.*** Antimicrob. Agents Chemother., 1969: 35-41, 1970.

Fardig, O.B., Rousche, M.A., Cabana, B.E., Moyland, D.S.: ***Purification of ampicillin.*** Brit., Med. J., P. 735, 1970.

Gessner, P.K., Cabana, B.E.: ***A study of the interaction of the hypnotic effect and the toxic effects of chloral hydrate and ethanol.*** J. Pharmaco. Exp. Ther., 174: 247-259, 1970.

Cabana, B.E., Gessner, P.K.: ***Determination of chloral hydrate, trichloroethanol, trichloroacetic and urochloralic acid in the presence of each other in tissue homogenates.*** Anal. Chem., 39: 1449-1452, 1967.

Gessner, P.K., Cabana, B.E.: ***Chloral acholate: Re-evaluation of its role in the interaction between the hypnotic effects of chloral hydrate and ethanol.*** J. Pharmacol. Exp. Ther., 1956: 602-605, 1967.

Gessner, P.K., Cabana, B.E.: ***The effect of ethanol on the kinetics of chloral hydrate metabolism in mice.*** Fed, Proc., 26: 568, 1967.

Cabana, B.E., Prokesch, J.C., Christiansen, G.S.: ***Study on the biogenesis of catecholamines in pheochromocytoma tissue culture.*** Arch. Biochem. & Biophysics, 106: 123-130, 1964.

Gessner, P.K., Cabana, B.E.: ***The effect of ethanol on chloral hydrate hypnosis in mice.*** Fed. Proc. Am. Soc. Exp. Biol., 3: 348, 1964.

ABSTRACTS:

Vetticaden, S.J., Cabana, B.E., Prasad, V.K., Purich, E.D., Jonkman, J.H., De Zeeuw, R., Braun, R.L., Leeson, L.J.: ***Development of a controlled release dextromethorphan hydrobromide "OROS" tablet: Steady state plasma levels and food effects.*** The Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii. D 06-W-19, pg. S66 , 1987.

Prasad, V.K., Vetticaden, S.J., Purich, E.D., Cabana, B.E., Scott, D.I., Karnes, H.T., Barr, W.H., Smith, H.L., Sica, D.A.: ***Dose proportionality study of toresamide, a new diuretic-Pharmacodynamic effect.*** The Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii. D 07-W-32, pg. S92, 1987.

Prasad, V.K., Cabana, B.E., Vetticaden, S.J., Purich, E.D., Braun, R.L.: ***Novel controlled release dextromethorphan formulations.*** The Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii. E 04-X-11, pg. S117, 1987.

Prasad, V.K., Cabana, B.E., Vetticaden, S.J., Purich, E.D., Braun, R.L.: ***Bioequivalency determination of an oral dextromethorphan liquid suspension.*** The Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii. D 07-W-01, pg. S84, 1987.

Cabana, B.E., Prasad, V.K., Vetticaden, S.J., Purich, E.D., Braun, R.L., Leeson, L.J.: ***Development of a controlled release dextromethorphan hydrobromide tablet: Evaluation of four "OROS" formulations.*** The Japanese-United States Congress of Pharmacetutical Sciences, Honolulu, Hawaii. D 06-W-18, pg. S65, 1987.

Cabana, B.E., Purich, E.D., Vetticaden, S.J., Jonkman, J.H.G., Prasad, V.K., Braun, R.L.: ***Phenotypic differences in dextromethorphan metabolism.*** The Eighty-Eighth Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics, Orlando, Florida. IC-4, pg. 5, 1987.

Cabana, B.E.: ***Dissolution testing as a regulatory requirement and predictor of in vivo bioavailability.*** Gothenburg, Sweden. August 2-3, 1986.

Itil, T.M., Cabana, B.E., Purich, E.D., Songar, A., Eralp, E.: ***Relative bioavailability following single oral doses of two generic products of diazepam relative to Valium® using both standard plasma levels and computer-analyzed EEG (CEEG) measurements.*** Int'l Symposium on Bioavailability and Bioequivalency, Dallas, Texas. May 19, 1985.

Cabana, B.E.: ***Bioavailability and pharmacokinetics in drug development.*** Sidney Riegelman Memorial Symposium, University of California, San Francisco, April 22-24, 1984.

Cabana, B.E., Purich, E.D.: ***Bioavailability assessment through multivariate analysis using pharmacokinetic parameters.*** 2nd European Congress of Biopharmaceutics and Pharmacokinetics, April 24-27, 1984, Salamanca, Spain.

Cabana, B.E., Purich, E.D.: ***Novel approaches for the assessment of bioavailability of psychotropic drugs.*** In Proceedings of the 14th Collegium International Neuro-Psychopharmacologicum Congress, Clin. Neuropharmacol., 7 (Suppl. 1), 372, 1984.

Cabana, B.E.: ***Bioavailability regulations and biopharmaceutics standards for controlled release drug delivery.*** In Proceedings 1982 Research and Scientific Development Conference, The Proprietary Association, Washington, D.C., 1983.

Cabana, B.E., Harter, J.G., ***Biopharmaceutic, clinical and toxicologic consideration in the evaluation of dermal and transdermal drug products.*** International Association for Pharmaceutical Technology, Munich, Germany, January 12, 1981. In ***Dermal and Transdermal Absorption.*** Ed. R. Brandau , B.H. Lippold. Wissenschaftliche Verlagsgesellschaft mbH, Stuggart, 1982.

Cabana, B.E., Purich, E.D., Hunt, J., Gummit, R., Leppick, I., Sawchuck, R.: ***Therapeutic plasma levels of phenytoin in epileptic patients as a function of absorption rate.*** Proceedings, First European Congress of Biopharmaceutics and Pharmacokinetics, Clermont-Ferrand, France, April 1, 1981.

Cabana, B.E., Purich, E.D., Rapaka, R.S., Schary, W.L., Prasad, V.K.: ***Biopharmaceutic considerations and new drug approval.*** World Conference on Clinical Pharmacology & Therapeutics, London, England, 1980.

Cabana, B.E.: ***Guidelines for evaluating the bioavailability of controlled release dosage forms.*** American Pharmaceutical Association of Pharmaceutical Sciences, Midwest Regional Meeting, Chicago, Illinois, May 1979.

Pitlick, W.H., Cabana, B.E., Meyer, M.C.: ***Absorption kinetics and bioavailability of 9 sustained-release papaverine products.*** APhA, Kansas City, MO, November, 1979.

Cabana, B.E.: ***The role of dissolution in new drug approval and assurance of drug bioavailability.*** The Swiss Pharmaceutical Society, Basel, Switzerland, April 1978.

Prasad, V.K., Alston, T.C., Shah, V.P., Campbell, K.M., Cabana., B.E.: ***In vitro/in vivo correlation of tetracycline hydrochloride capsules.*** APhA, New York, May 1977.

Dighe, S.V., Cabana, B.E., Prasad, V.K.: ***In vitro/in vivo correlation of tetracycline hydrochloride tablets and capsules - Part III: Bioequivalence establishment.*** APhA, New York, May 1977.

Hunt, J.P., Shah, V.P., Prasad, V.K., Cabana, B.E.: ***In vitro dissolution specification for dihydroergotoxine sublingual tablets.*** APhA, New York, May 1977.

Shah, V.P., Hunt, J.P., Prasad, V.K., Cabana, B.E.: ***In vitro/in vivo correlation of tetracycline hydrochloride tablets and capsules - Part II: Bioequivalence specifications.*** APhA, New York, May 1977.

Prasad, V.K., Cabana, B.E., Hunt, J.P., Furman, W.B., Cox, D., Wells, C., Wood, J.: ***Bioequivalency establishment of marketed digitoxin tablets - Part II: Establishment of in vitro bioequivalence standard.*** APhA, Phoenix, Arizona, November 1977.

Prasad, V.K., Hunt, J.P., Cabana, B.E., Wagner, J.G.: ***Establishment of bioequivalency of 5 mg prednisone and prednisolone tablets - Revised in vitro dissolution specification.*** APhA, Phoenix, Arizona, November 1977.

Cabana, B.E., Van Harken, D.R.: ***Comparative metabolic and pharmacokinetic studies in cephapirin in man.*** 126th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1972.

Cabana, B.E., Van Harken, D.R.: ***Comparative metabolic and pharmacokinetic studies in cephapirin in laboratory animals and man.*** Proc, of 5th International Congress of Pharmacology, P. 35, 1972.

Cabana, B.E., Van Harken, D.R., Dittert, L.W., Doluisio, J.T.: ***Kinetic analysis of cephapirin absorption, distribution and elimination in man.*** 12th Interscience Conference on Antimicrobial Agents and Chemotheraphy, 1972.

Cabana, B.E., Taggart, J.T.: ***Comparative pharmacokinetics of BB-K8 and kanamycin in dog and man.*** 12th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1972.

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